Neuromodulation of Conscious Perception: Investigating Thalamic Roles through Ultrasonic Stimulation

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General Goal

The overarching aim of this study is to investigate the impact of transcranial low-intensity focused ultrasound pulsation (LIFUP) on conscious perception. Our central hypothesis is that specific subcortical brain areas play pivotal roles in conscious perception, and by altering neural activity in these regions, we can uncover their distinct contributions. To test this hypothesis, we will employ both psychological assessment and noninvasive brain stimulation techniques. In particular, we will evaluate perceptual outcomes using a near-threshold perceptual task, employing Signal Detection Theory (SDT) metrics. Concurrently, we will utilize LIFUP to stimulate select subcortical brain regions and assess their causal influence during conscious perception.

This research serves two critical purposes. First, it contributes to our understanding of the neural underpinnings of consciousness—a fundamental and unresolved issue in neuroscience. Second, from a clinical perspective, the findings hold promise for potential applications of LIFUP in medical settings, such as facilitating the recovery of consciousness during the emergence from anesthesia.

Introduction

The neural mechanisms underlying conscious perception have long intrigued the field of neuroscience [1–16]. While extensive research has focused on the cortical aspects of conscious perception [6,7,15], the role played by subcortical structures has received relatively little attention. Among various important subcortical sites, such as brainstem and basal forebrain nuclei [17], the thalamus stands out as a critical structure due to its extensive bidirectional connections and interactions with the cerebral cortex [18,19].

Within the thalamus, two major cell classes exist, known as "core" and "matrix" cells [20,21]. These cells project differently to the cortex. The human thalamus can be coarsely divided based on the prevalence of these two cell types (**Figure 1**). Core cells are preferentially distributed in the posterior thalamic areas, while matrix cells are more abundant in the anterior regions [22]. Core cells primarily innervate the granular layers of the cerebral cortex, sending axonal projections to Layers III and IV of sensory cortices in a retinotopic, tonotopic, and somatotopic manner. In contrast, matrix cells innervate the supragranular cortex in a relatively diffuse manner, indicating a preference for interactions with higher-order cortical areas [22]. Understanding the distinct roles of these thalamic cell classes could significantly contribute to unraveling the mysteries surrounding conscious perception.

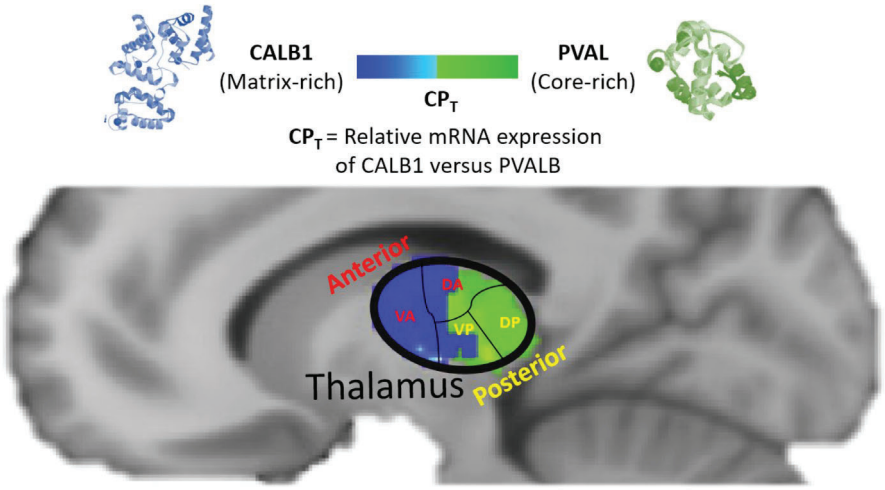

Figure 1. *The distribution of two distinct sub-populations of thalamic projection cells (core and matrix). The cell types were identified based on mRNA expression levels of two calcium-binding proteins, Calbindin (CALB1) and Parvalbumin (PVALB), as provided by the Allen Human Brain Atlas [23]. The relative weighting of the CALB1 and PVALB level differences was measured using the CP_T metric [22], where blueish values indicate regions with higher CALB1 levels (matrix-rich), and greenish values indicate areas with higher PVALB levels (core-rich). The thalamus is coarsely divided into four sections: ventral anterior (VA), dorsal anterior (DA), ventral posterior (VP), and dorsal posterior (DP).*

To investigate the functional role of thalamic areas in conscious perception, it becomes imperative to causally alter their activity. Traditional brain stimulation methods either involve invasive procedures or have low target resolution. For instance, deep-brain stimulation involves surgically implanted electrodes whereas transcranial magnetic stimulation suffers from low spatial resolution. Optogenetic approaches offer unparalleled precision but require genetic manipulation, making them unsuitable for use in humans.

The novel method of transcranial low-intensity focused ultrasound pulsation (LIFUP) as an attractive alternative that overcomes these limitations. LIFUP has the unique ability to non-invasively target deep brain nuclei, including specific thalamic areas, with remarkable precision of sonication focus [24]. Despite the growing body of literature on LIFUP-induced behavioral modifications [25], its effect on conscious perception remains largely unexplored. Employing LIFUP to noninvasively modulate the activity of select brain regions has the potential to shed light on the intricate neural mechanisms of conscious perception in humans.

Research Objectives

The primary objective of this study is to investigate the causal role of thalamic areas in conscious perception using LIFUP. We hypothesize that stimulating different thalamic regions by LIFUP will result in distinct perceptual outcomes, potentially affecting subjective perception as quantified by criterion and detection sensitivity as described in detail under Data Analysis and Statistics.

To test these hypotheses, we have devised a three-fold approach:

1. We will conduct a near-threshold perceptual task to assess the perceptual outcomes under different conditions.

2. Utilizing transcranial LIFUP, we will selectively stimulate (both excite and inhibit) the anterior and posterior thalamic areas. These areas are chosen because they are known to be differentially enriched by matrix and core thalamic cells, respectively.
3. We will evaluate the quality of conscious contents using two orthogonal quantities derived from Signal Detection Theory: criterion (c) and sensitivity (d'). Criterion (c) represents a subject's tendency to report subjective recognition of a target stimulus, irrespective of its presence or absence. On the other hand, sensitivity (d') measures a subject's ability to differentiate between trials with a target present and trials with a target absent (**Figure 2**).

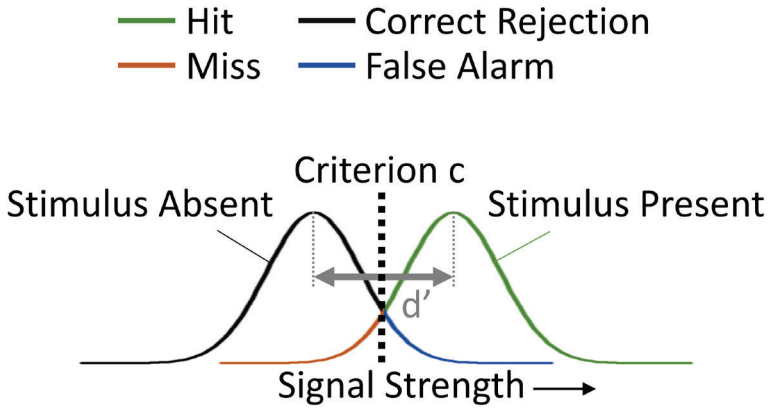

***Figure 2**. An overview of Signal Detection Theory*

We expect that exciting the matrix cell-rich areas of the thalamus, such as the ventral anterior section, will lead to a decrease in criterion (c), indicating a shift of the decision criterion towards a more liberal response bias. Conversely, exciting the core cell-rich areas of the thalamus, like the dorsal posterior section, will increase sensitivity (d'), resulting in improved differentiation ability in stimulus perception. Conversely, we also anticipate that inhibiting the ventral anterior thalamus will have the opposite effect on criterion (c), leading to a more conservative decision bias. Inhibiting the dorsal posterior thalamus will reduce sensitivity (d'), resulting in a decreased ability to differentiate between stimuli. By observing these effects, we aim to unravel the distinct causal roles of the anterior and posterior thalamus in conscious perception. This disentanglement will provide valuable insights into the mechanisms of specific thalamic regions in shaping perceptual processes.

Number of Subjects, Recruitment and Informed Consent

Our study will involve the enrollment of 60 participants, who will be randomly assigned to two groups, with each group consisting of 30 participants. The participants will be divided based on the type of transcranial LIFUP they will receive, either excitation or inhibition, targeting four specific thalamic areas. See experimental design details below. Healthy participants will be recruited by listing on UMClinicalStudies.org and by postings at area colleges and community groups in Ann Arbor. Interested volunteers will call the phone number of a designated recruiter for an initial phone screening. The initial phone screening will consist of questionnaires related to medical history, demographic information, handedness, inclusion and exclusion criteria. If interested, the participant will

complete the questionnaires, which will be reviewed by the study team. Once eligibility is confirmed by the study team, the one-time research study session will be scheduled. Participants may be screened for COVID-19 prior to entry into the hospital per hospital guidelines.

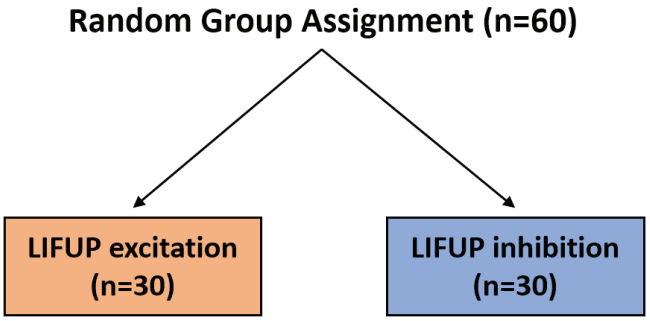

Figure 3. *Randomized study group assignment. A total of 60 participants will be enrolled in the study and randomly assigned to two groups, each comprising 30 participants. The group assignment will be based on the type of transcranial LIFUP they will receive, either in the form of excitation or inhibition.*

All participants will give written informed consent according to institutional guidelines prior to any testing. The Principal Investigators or their designee will obtain consent using a written consent form approved by the Institutional Review Boards of the University of Michigan Medical School (IRBMED). It will contain detailed information regarding the purpose, risks and benefits of participating. Copies of the signed consent form will be given to the subjects; the original consent will remain with the study team.

Compensation

Participants will be compensated $100 for completing the one-time visit. Participants who have shaved or no hair, or those willing to shave the right side of their temple will be compensated an additional $75. Participants who are willing to shave an area around their right side of their temple should do this prior to arriving to their scheduled study visit.

Inclusion and Exclusion Criteria

Volunteers are screened using a medical history and demographics questionnaire.

Inclusion Criteria:

- Healthy adults ages 18 – 40.
- Must be right-handed.
- Must have normal or corrected-to-normal vision (while wearing contact lenses).
- Must not be on any medications for any neurological, psychological, or psychiatric conditions.
- Must be English speaking.
- Must be capable of giving written informed consent.

Exclusion Criteria:

- Vision that is not 20/20, or vision that is not corrected to 20/20 while wearing contact lenses.
- History of significant head injury with loss of consciousness.
- Learning disability or other developmental disorder.
- Any impairment (sensory or motor loss), activity, or situation that in the judgment of the study coordinator or Principal Investigators would prevent satisfactory completion of the study protocol.

Methods and Procedures

LIFUP Method. The mechanism of action of LIFUP have been associated with mechanically induced changes in membrane capacitance, cavitation events, and mechanical sensitivity of voltage-gated ion channels [26–28]. A neuronal intramembrane cavitation excitation model [29,30], which accounts for differential effects as a function of cell-type, emerged as an explanation for the stimulus parameter-dependent range of excitatory vs. inhibitory effects. In this model, the LIFUP parameter duty cycle (DC) likely determines excitation (higher DC, allowing for longer sonication-on periods) and inhibition (lower DC, allowing for short ultrasonic bursts with longer periods between bursts) independent of the other sonication parameters. Excitation occurs optimally at a high duty cycle of 70%, allowing for a trade-off in regular-spiking and fast-spiking neurons between charge accumulation during the ultrasound and discharge during the off periods of ultrasound [25]. In contrast, a low duty cycle (e.g., DC < 10%) produces a suppressive effect [31–39]. Thus, LIFUP can bidirectionally modulate the circuitry of interest depending on the choice of duty cycle.

We will utilize the BrainSonix BXPulsar 1002 LIFUP System (BrainSonix Inc. http://www.brainsonix.com/). FDA has determined that our proposed clinical investigation is a nonsignificant risk (NSR) device study because it does not meet the definition of a significant risk (SR) device under 21 CFR 812.3(m) of the investigational device exemptions (IDE) regulation (21 CFR 812). An IDE application is not required to be submitted to, or approved by, FDA for a NSR study. This device contains a single-element, air-backed, spherical section ultrasound transducer with 61 mm diameter and 80 mm focal depth. The transducer is mounted in a plastic housing filled with deionized, de-gassed water and sealed with a thin polyethylene membrane permeable to ultrasound. The transducer will be coupled to the scalp of the participant using a 3D-printed transducer holder that allows for sonication to occur in conjunction with ultrasonic standoff pads and ultrasound gel. The LIFUP system operates at a fundamental frequency of 650 kHz. Following previous work, we plan to administer a pulse repetition frequency of 10 Hz, pulse width of 0.5 ms, and a duty cycle of 70% to induce an excitatory effect and a duty cycle of 5% to induce a suppressive effect. For each thalamic area, a total of 10 sonications (in 10 minutes) will be administered, with a derated spatial-peak temporal-average intensity (Ispta) of 720 mW/cm^2, each lasting 30 s, separated by 30 s pause intervals (**Figure 4**). We will utilize the Brainsight Navigation system, developed by Brainbox Ltd, to ensure precise targeting and positioning of the transducer. At the target location, the estimated peak pressure will be 0.71 MPa, and the ultrasound beam width will be 5 mm. The estimated targeting accuracy (uncertainty) at the desired location is ±2.5 mm. Electromyography (EMG) recordings will complement the behavioral data, providing valuable information about muscle activity and response patterns during the

study.

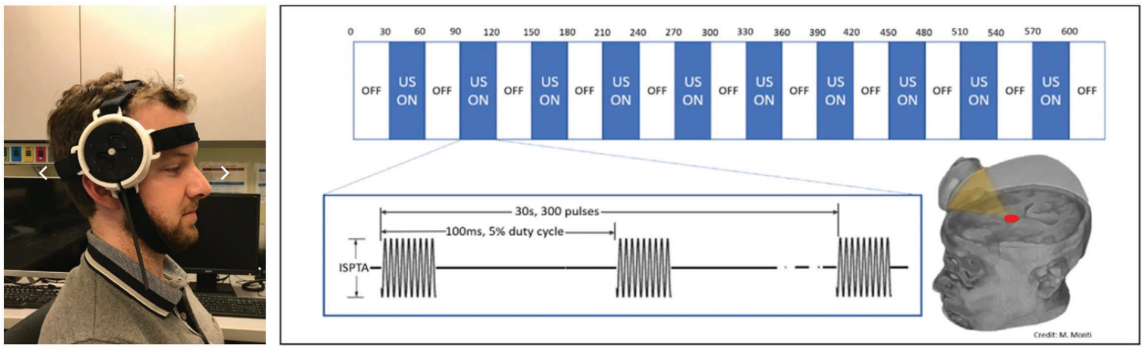

Figure 4. *Conceptual illustration of LIFUP setting and parameter configuration (adapted from* [33] *and https://brainsonix.com/technology/).*

Experimental Design. The experimental will consist of a 10-minute baseline period (LIFUP-OFF) followed by four 10-minute sessions of stimulating (LIFUP-ON) four thalamic areas. The order of thalamic area stimulation will be counterbalanced across participants and will include the ventral anterior (VA), dorsal anterior (DA), ventral posterior (VP), and dorsal posterior (DP) sections of the thalamus. The center coordinates of these thalamic regions will be derived from a previous study on thalamic parcellation [40]. Given that previous studies have not indicated any functional lateralization of the thalamic areas, we will target only the left hemisphere for the sake of convenience in this study.

Perceptual Task. The quality of conscious perception will be assessed by a well-established psychometric approach, the near-threshold perceptual task [41,42]. This task allows one to compare the neural activity evoked by identical weak stimuli that are sometimes perceived and sometimes remain subliminal (**Figure 5**). It thus rules out potential confounds of variability derived from the differences in physical property of the stimuli. All stimuli will be programmed using E-Prime (Psychology Software Tools, Pittsburgh, PA) and delivered via a laptop computer. Stimuli will be presented at the threshold of subjective recognition. An adaptive thresholding procedure will be conducted whereby image contrast will be titrated to reach a 50% subjective recognition rate for each subject. Stimuli will include two common visual object categories: faces and houses. Participants' task is to report the category ("F" or "H") of an image presented and their recognition experience ("Yes" or "No"). Specifically, they will be instructed to report the object category regardless of their recognition experience and, in cases of unrecognized images, to make a genuine guess (two-alternative choice discrimination). Then, they will be instructed to report whether they see an object, such that even if the object appears unclear or noisy, they should respond "yes", but if they see nothing or only low-level features, they should respond "no".

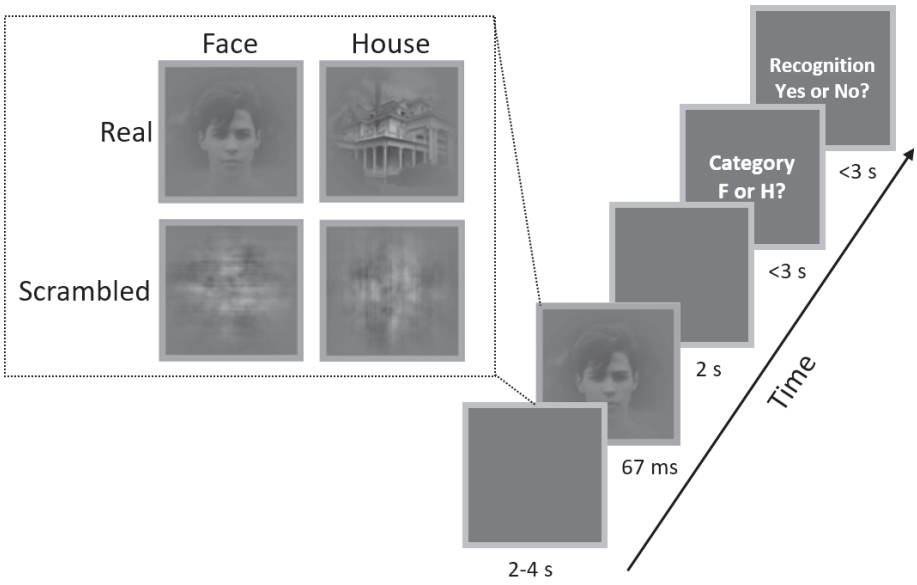

Figure 5. *Visual task design. During each 10-min session, participants will complete an image recognition task. Stimuli (faces, houses, and scrambled images) will be presented at the threshold of subjective recognition. Participants' task is to report the category ("F" or "H") of the image presented and their recognition experience ("Yes" or "No").*

The stimulus set will include real and scrambled images, the latter will be created by phase-shuffling of a randomly chosen real image from each category to preserve category specific low-level image features [41,42]. Because scrambled images serve as "catch trials" to determine the subjects' baseline tendency to give positive responses to a question about their recognition experience. The pre-stimulus interval will vary randomly from trial to trial between 2 and 4 seconds to prevent stimulus timing predictability. The stimuli will be presented in a randomized order to prevent category predictability.

Primary Outcome Measure

Perceptual criterion (c) and sensitivity (d') derived from the Signal Detection Theory (SDT) analysis. These measures will be assessed over a timeframe spanning from the baseline to 60 minutes after the LIFUP stimulation.

Data Analysis and Statistics

For each 10-min session, we will calculate sensitivity (d') and criterion (c) using subjective reports of recognition as "yes" or "no". (d') indicates the ability to discriminate between real and scrambled images. It is computed by subtracting the z-transformed False Alarms Rate (FAR) from the z-transformed Hit Rate (HR): d' = Z(HR) - Z(FAR)), where Z is an inverse normal cumulative distribution function. (c) reflects the tendency to make "yes" reports to indicate recognition, regardless of whether the stimulus is a real or a scrambled image, which is computed as: c = -0.5 x (Z(HR)+Z(FAR)). We will also calculate percent of correct responses as an operational measure of two alternative-forced-choice sensitivity using subjective category reports, i.e., responses to the first question: "Face" or "House".

We will conduct a repeated-measures ANOVA, considering measurements taken during both the baseline and the four thalamic areas' stimulation sessions. This analysis will be

performed at the group level to assess the effects of LIFUP on the perceptual measures. To determine statistical significance, we will apply a false discovery rate (FDR) correction and set the threshold at $\alpha < 0.05$. This approach will help us identify any significant differences between the baseline and the different thalamic area stimulations in terms of sensitivity (d') and criterion (c).

Anticipated Results and Interpretation

We expect to observe differential changes in the perceptual outcomes based on the LIFUP stimulation of different thalamic areas. We anticipate that stimulation of the ventral anterior thalamus will decrease criterion (c), indicating a shift of the decision criterion in the liberal direction. During exciting the dorsal posterior thalamus, we expect an increase in sensitivity (d'), reflecting a higher sensitivity in differentiating between stimuli. Conversely, when inhibiting the ventral anterior thalamus and the dorsal posterior thalamus, we expect the opposite effects on criterion (c) and sensitivity (d') compared to the outcomes seen during their respective excitations. The effects of stimulating the dorsal anterior thalamus and the ventral posterior thalamus are expected to lie between the effects of ventral anterior and dorsal posterior thalamic stimulation. These findings should provide valuable insights into the specific contributions of these thalamic regions in shaping conscious experiences.

Power Analysis

We considered a recent review article that summarized 25 LIFUP studies in humans. These studies had sample sizes ranging from 1 to 50, with a median value of 16. Since the neuromodulation effect is dependent on various factors, such as parameter settings and specific brain regions targeted, determining a prior effect size is challenging. However, we have planned a subject number of 30 per group, which exceeds the median sample size reported in the literature. With a larger sample size, we aim to enhance the statistical power, reliability and sensitivity of our findings, enabling us to draw robust conclusions about the neuromodulatory effects of LIFUP on conscious perception.

Biological Variables

Our participant recruitment will be inclusive, encompassing individuals of all sexes and diverse ethnic/racial backgrounds, with the goal of achieving equal representation and promoting diversity. However, to minimize age-dependent variation in LIFUP effects, the age range of participants will be restricted to 18-40 years. This limitation will help ensure a more homogeneous sample for our study, enabling us to focus to reliably determine specific effects of LIFUP on conscious perception within the limitation of sample size.

Human Studies and Safety Profile related to LIFUP

LIFUP has been shown to be a safe and effective method to modulate human brain activity, when the stimulation parameters and protocol follow the available guidelines [24,43,44]. The majority of studies with ultrasound have reported no adverse events or evidence of anatomical damage [35,45–50]. Mild and moderate symptoms have been occasionally reported, such as neck pain, sleepiness, muscle twitches, itchiness, and headaches [51]. However, a comprehensive safety survey focusing on ultrasound for human neuromodulation found no evidence of serious adverse effects in a large cohort

of participants[52]. Out of 120 participants, 64 responded to a follow-up questionnaire, and none experienced serious adverse effects. Only 7 out of the 64 participants reported mild to moderate symptoms (e.g., neck pain, attention problems, muscle twitches, and anxiety) that were perceived as 'possibly' or 'probably' related to their participation in LIFUP experiments. Notably, common unrelated symptoms included sleepiness and neck pain. Initial transient reports of mild neck pain, scalp tingling, and headaches were extinguished upon follow-up, with no new symptoms reported up to one month after the study [52]. Furthermore, studies have not shown any LIFUP-induced tissue damage in the absence of heating, except in cases where contrast agents were used to enhance cavitation effects [26]. Additionally, LIFUP has been shown to be safe even at intensities several times higher than the FDA limit for diagnostic ultrasound (720 mW/cm^2) [53]. Overall, the available evidence indicates that LIFUP is a safe and well-tolerated method for human neuromodulation, provided the proper guidelines and parameters are followed.

Justification for the Risks Involved

The proposed procedure entails minimal risks, while the potential knowledge gains hold significant importance for humanity. As a result, the risk-to-benefit ratio is very low. These experiments offer a unique opportunity to understand the neuromodulation's impact on human conscious perception. The potential insights gained from this study justify the minimal risks involved, making it a valuable and worthwhile endeavor.

Procedures for Minimizing Risks

All research subjects will undergo a thorough screening process to ensure they meet the inclusion and exclusion criteria. Additionally, if any subjects express or exhibit anxiety related to the LIFUP procedure, they will have the opportunity to discuss their feelings or withdraw from the experiment if they wish.

We are committed to strictly adhering to the FDA limit for diagnostic ultrasound intensity (as outlined in the FDA guidance document on diagnostic ultrasound systems and transducers) during the LIFUP procedure to maintain safety and prevent any adverse effects. The FDA previously determined that the use of LIFUP in our studies carries nonsignificant risk (NSR).

Adverse Events

Adverse events will be monitored throughout the procedures and for 24 hours after the procedure via a phone call to the subjects. We will follow their medical record for 30 days following the procedure. Complications or adverse events that are observed by the investigator or reported by the subject will be recorded. For all adverse events and complications, a description of the event, date first observed, any action taken, and ultimate outcome will be recorded.

For all adverse events, sufficient information will be pursued and/or obtained as to permit 1) an adequate determination of the outcome of the event (i.e., whether the event should be classified as a serious adverse event) and; 2) an assessment of the causal relationship between the adverse event and the investigational device, or if applicable, the other study treatments of diagnostic product(s). Adverse events felt to be associated with the investigational device, or if applicable, other study treatment or diagnostic product(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or

stabilizes at a level acceptable to the sponsor-investigator. Adverse events will be reported to the IRB according to their reporting guidelines.

Serious and Unanticipated Adverse Device Events

An unanticipated adverse device event is defined as “any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects.

The sponsor-investigator will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the investigational device or, if applicable, other study treatment of diagnostic products(s) and 3) if the adverse event meets the criteria for a serious adverse event. The sponsor shall promptly report the results of an evaluation of any serious and unanticipated adverse event to the FDA, the University of Michigan IRBMED, and participating investigators (if any) as soon as possible, but not later than 10 working days after the sponsor first receives notice of the effect.

Confidentiality

Strict subject confidentiality will be maintained. Subjects will be assigned a code number following their first contact in the protocol. This number will be used throughout the experiment and will be the only data identifier. The identity of subjects will not be revealed at scientific meetings, in publications or other vehicles of public communication. Data will be pooled across subjects where appropriate. Only the PIs, Co-investigators, and the study coordinator will have access to the ID code, which will be stored in a locked file separate from the data.

Data collected on the subjects will be coded by study ID numbers and entered directly into notebook computers used in the field. These computers are password protected and stored behind a locked door when not in use. Clinical and biographic data are entered into the database using the ID number only. Only select staff members have access to the actual paper copies. Medical information will be released by name only to health care providers, and then only with written permission from the subject.

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